

The pathology of the human locus ceruleus

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Abstract. The number of nerve cells of locus ceruleus and their nucleolar volume were determined in 63 normally aged individuals and in 41 cases with neurologic diseases. Pathologic alterations, such as a severe nerve cell loss and atrophy with or without extensive neurofibrillary degeneration or Lewy body formation, were generally seen in the nucleus locus ceruleus in Alzheimer's disease, Down's syndrome, dementia pugilistica, Parkinson's disease, and progressive supranuclear palsy, but such changes were only slight in normally aged individuals and minimal in motor neuron disease. Protein synthetic capacity was substantially reduced in the remaining nerve cells of the locus ceruleus, in Alzheimer's disease, Down's syndrome, and dementia pugilistica, but was unaltered in normally aged individuals (even in extreme old age), in motor neuron disease, and in the few remaining cells in Parkinson's disease and progressive supranuclear palsy. It is suggested that the pathologic alterations in the locus ceruleus found in these diseases, in conjunction with changes in the hypothalamus, lead to impairment of mental ability with eventual dementia through disturbance of the function of those pathways regulating homeostasis within the central nervous system.

Key Words: locus ceruleus - degeneration - dementia

Introduction

Within the brain stem of the mammalian CNS there are groups of nerve cells that are unusual in as much as they employ norepinephrine as neurotransmitter and with age accumulate the lipoprotein pigment, neuromelanin. The major group of such cells constitutes the locus ceruleus and in several species examined gives rise to ascending pathways innervating all areas of the cerebral cortex [Ungerstedt 1971, Kobayashi et al. 1974, Bates et al. 1977, Crow et al. 1978], cerebellum [Olsen and Fuxe 1971], and certain regions of the hypothalamus, particularly the paraventricular and supraoptic nuclei [Kobayashi et al. 1974, Versteeg et al. 1976, Bates et al. 1977]. Descending pathways [Nygren and Olsen 1977] project to the dorsal motor nucleus of the vagus nerve and sacral spinal cord [Westlund and Coulter 1980]. These pathways seem broadly matched in humans [Pearson et al. 1979]. Indeed, it appears from these studies that a single neuron can innervate areas of cerebrum, cerebellum, and even spinal cord.

Although the neuroanatomy of this group of cells is becoming increasingly clear and experimental studies have suggested that the locus might influence higher order functions, including learning and memory consolidation [Stein et al. 1975, Zornetzer et al. 1978], arousal [Clark 1979], attention, and reward [Crow et al. 1978, Mason and Ivesen 1978], a clear clinical counterpart of their disease in humans still remains unrecognized. In this report changes in function of nerve cells of locus ceruleus are reported in cases of normal ageing and in others with neurologic illness.

Materials and methods

Brains were obtained at autopsy from 104 patients, and these were fixed in 10% neutral formalin. Paraffin sections were cut at 5- μ m thickness from blocks of representative areas and stained by conventional neuropathologic techniques.

In 63 cases there were no significant neuropathologic findings, except that in certain of the more elderly cases there were minimal amounts of cerebral softening or a few Alzheimer type changes, or both. None of these 63 cases suffered

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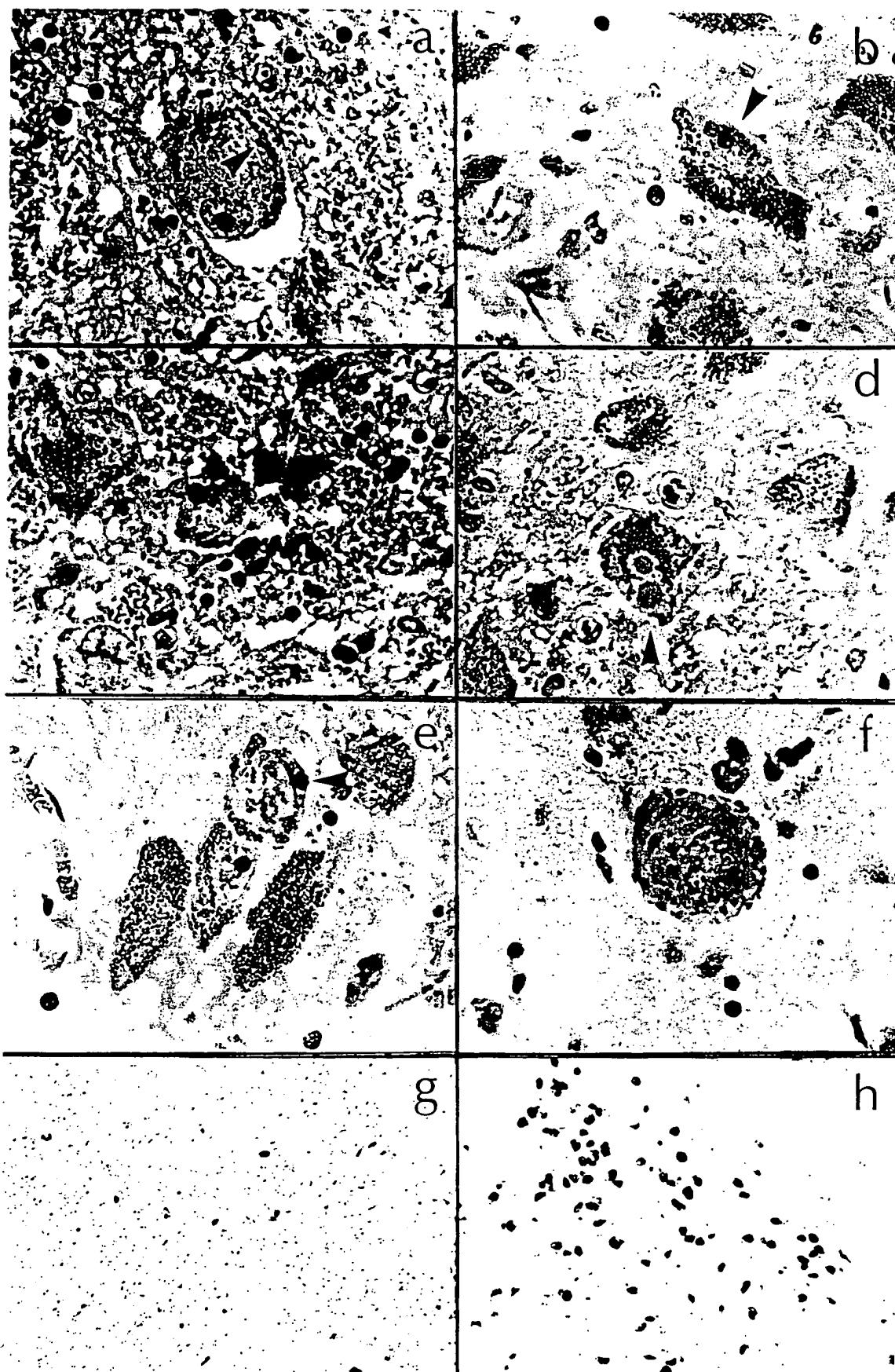


Fig. 1 The human locus ceruleus in control subjects (a) 20 years of age showing nerve cells to contain little neuromelanin but large amounts of cytoplasmic RNA and a large open nucleus with strongly basophilic nucleolus. Other controls (b)–(f) of over 80 years of age show atrophic cells (b), with heterolysis by macrophages (c), or cells containing Lewy bodies (d), globose neurofibrillary tangles (e), or appear as ghost cells (f). Severe loss and atrophy of nerve cells of the locus ceruleus is seen in an 83-year-old subject with Alzheimer's disease (g) when compared with a control subject (h) of that age. (a)–(e) Weigert Haematoxylin-Eosin, $\times 450$; (f)–(h): Azure B, $\times 60$, $\times 60$, $\times 60$, respectively.

from neurologic or psychiatric illness, and these were defined as age controls.

Every one of the other 41 cases showed clinical histories and neuropathologic alterations characteristic of the particular disorder (details of which are not presented in this paper). The 41 cases were grouped as follows:

Alzheimer's disease: 19 cases, age range 80–92 (mean 84.7 ± 1.0 years);

Down's syndrome: 1 case, age 59 years;
dementia pugilistica: 4 cases, ages 50, 55, 59, and 62 (mean 55.2 ± 1.0 years);

idiopathic Parkinson's disease: 6 cases, ages 34, 66, 69, 70, 71, and 71 (mean 65.7 ± 7.5 years);

progressive supranuclear palsy: 3 cases, ages 41, 64, and 69 (mean 56.0 ± 7.5 years); and

motor neuron disease: 8 cases, age range 39–77 years (mean 57.9 ± 2.2 years).

In all 104 cases 5 paraffin sections of 20- μ m thickness were cut at 100- μ m intervals from that block of brain stem containing the locus ceruleus. These were stained using Azure B after the method of Shea [1970]. The number of nucleolated nerve cells of locus ceruleus in these sections were counted [Tomlinson et al. 1981] and their nucleolar volume measured [Mann and Yates 1979] also.

Neuropathologic observations

Controls

In young adults nerve cells of the locus ceruleus are seen to contain large amounts of cytoplasmic RNA, and the nucleolus is prominently stained within a large open nucleus that shows finely granular chromatin. Only small quantities of neuromelanin are present within the cell body at this time (Fig. 1a). Although from middle age onward most cells show no apparent change in

structure, except that of increased melanin pigmentation, others are atrophied, with the number of such cells increasing with age. Atrophied cells are characterized by shrinkage of the cell body with a reduction in the amount of cytoplasmic RNA and in the size of the nucleus and nucleolus (Fig. 1b). Eventual heterolysis of these cells by macrophages results in aggregations of residual melanin being freely deposited within the neuropil or within these latter cells (Fig. 1c). In a few of the more elderly cases, isolated cells contained Lewy bodies (Fig. 1d), others contained globose neurofibrillary tangles (Fig. 1e), and "ghost cells" with only tangle material, and melanin granules (Fig. 1f) were also seen.

Patients

Histologic changes in locus ceruleus, such as gross depigmentation caused by severe loss and atrophy of nerve cells (Fig. 1g) together with a greater incidence of remaining cells containing Lewy bodies, or neurofibrillary tangles, or appearing as ghost cells, were noted to differing extents in the various conditions, as summarized in Table 1. In no case were significant alterations in blood vessels or in glial cells noted in the region of the locus.

Results

Values of mean number per 20- μ m section of nucleolated nerve cells of locus ceruleus for all 63 control cases were related to age by linear regression analysis (Fig. 2a). The number of nerve cells (y) is significantly decreased with age (x): ($y = 109.3 - 0.4x$; $r = 0.413$; $p < 0.001$) by 0.36% per annum. This is similar to findings of Vijayashankar and Brody [1979], who counted nucleolated nerve

Table 1 Summary of pathologic alterations in locus ceruleus in 41 cases of disorders as shown.

	Nerve cell loss	Nerve cell atrophy	Depigmentation	Lewy bodies	Neurofibrillary tangles	Ghost cells
Senile dementia of Alzheimer type	++	++	++	—	+	—
Down's syndrome	+++	+++	+++	—	++	+
Dementia pugilistica	++	+++	++	—	++	+
Parkinson's disease	+++	+	+++	++	—	—
Progressive supranuclear palsy	++	+	++	—	+++	++
Motor neuron disease	—	—	—	—	+	—

— indicates absent; + rare or slight; ++ common or severe; +++ numerous or extreme.

(a), globose neurofibrillary tangles (e), or appear as ghost cells (f). Severe loss and atrophy of nerve cells of the locus ceruleus is seen in an 83-year-old subject with Alzheimer's disease (g) when compared with a control subject (h) of that age. (a)–(e) Weigert Haematoxylin-Eosin, $\times 450$; (f)–(h) Azure B, $\times 450$, $\times 60$, $\times 60$, $\times 450$, $\times 60$, $\times 60$, respectively.

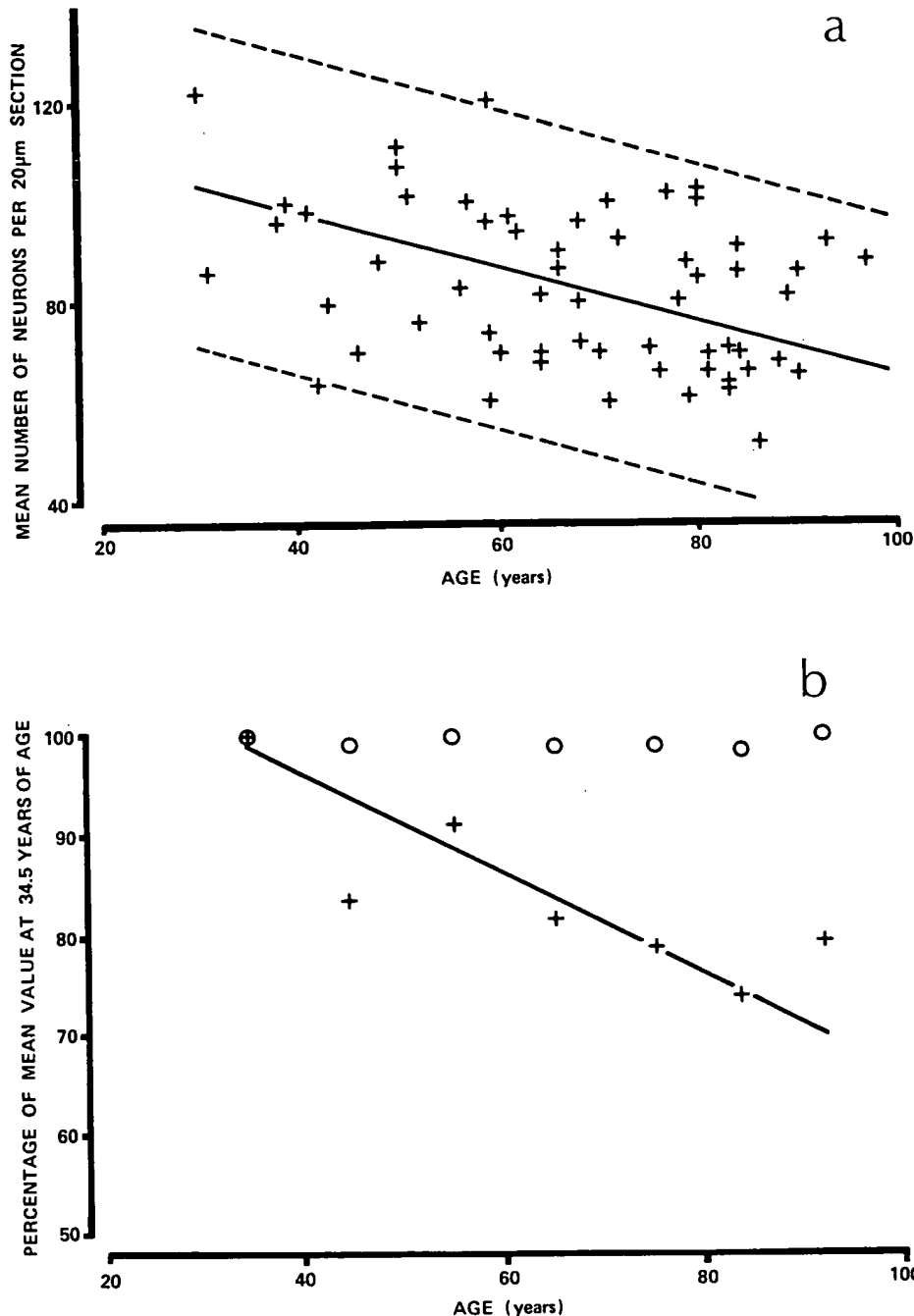


Fig. 2 Graphs of (a) mean number of nucleolated nerve cells of locus ceruleus per 20-µm section, plotted against individual age, for 63 control cases; (b) mean percentage number of nerve cells (+) and of nucleolar volume (O), plotted against mean age, for the 63 controls, grouped into 10-year class intervals.

cells in every 10th section throughout the locus ceruleus. Analysis of their data from 23 cases between ages 31 and 87 years inclusively shows that total cell counts (y) fell significantly with age (x): ($y = 24175.2 - 157.5x$; $r = 0.706$; $p < 0.001$) by 0.35% per annum. Tomlinson et al. [1981] also reported a decline in nerve cell number with advancing age in a smaller number of cases.

Mean values of nerve cell number and nucleolar volume from the 63 cases were pooled by age into

10-year classes, and the overall mean value for each age group was calculated. These values were expressed as percentage of that of the 30–40 year class and related to mean class age as in Fig. 2b. Nerve cell number is progressively reduced with age, such that by the 9th decade about 25% of nerve cells have been lost from the locus ceruleus. However, even at this age nucleolar volume is maintained within 98% of the youngest value in those 75% of cells that remain (Fig. 2b).

Data from all 63 cases were therefore pooled and the overall mean nucleolar volume calculated to be $68.8 \pm 0.7 \mu\text{m}^3$.

Precise compensation for the effects of age alone in the disease cases, which are superimposed on any possible changes due to the disease process, was not possible by exact matching for age of patient and control groups. Therefore, the number of nucleolated nerve cells *expected* at any particular age was calculated for all patients within each disease group by reference to the linear regression obtained from the control group data. The number of nerve cells *observed* in any case was then subtracted from its expected number; such values were pooled by group (Table 2) and the overall mean difference for each patient group was tested for significance by reference to *t* distribution. In this way the observed number of nerve cells in the locus ceruleus is *significantly reduced* for patient age (Table 2) in the cases of Alzheimer's disease (55%), Down's syndrome (95%), dementia pugilistica (66%), Parkinson's disease (79%), and progressive supranuclear palsy (51%), but is unchanged in motor neuron disease.

Nucleolar volume of (remaining) cells of the locus ceruleus is also significantly reduced in Alzheimer's disease (18%), Down's syndrome (27%), and dementia pugilistica (26%) (Table 2).

No significant alteration in nucleolar volume was measured in remaining cells in Parkinson's disease, progressive supranuclear palsy, or in motor neuron disease (Table 2).

Discussion

Nerve cells of the locus ceruleus form a widespread nerve network whose fibers mainly *termi-*

nate on capillary walls within the brain [De la Torre 1976, Swanson et al. 1976]. The locus ceruleus receives principal *afferent pathways* from the hypothalamus particularly the *supraoptic and paraventricular nuclei* [Swanson and Hartman 1980] and *from the periphery via the vagus nerve* [Takigawa and Mogenson 1977, Svensson and Thoren 1979]. Electrical stimulation of the locus ceruleus results in a reduction in cerebral blood flow [Raichle et al. 1975, De la Torre 1976, Katayama et al. 1981], an increased water permeability [Raichle et al. 1975], and a decreased deoxyglucose uptake [Abraham et al. 1979]. Destructive lesions increase blood flow [Bates et al. 1977]. Activation of the vagus nerve input through either electrical stimulation [Takigawa and Mogenson 1977] or blood volume loading [Svensson and Thoren 1979] exerts an inhibitory influence over function of the locus ceruleus. Conversely, there is increased activity in neurons of the locus ceruleus following experimental hemorrhage [Bubenik and Monner 1972]. These findings suggest that pathways between the locus ceruleus and the hypothalamus may monitor intracerebral responses to altered conditions in the periphery via parasympathetic and pituitary contacts particularly in respect to *cardiovascular function*. Essentially they would maintain homeostasis within the CNS against adverse changes in the periphery; cells of the locus ceruleus would contribute a resting tone to the intraparenchymal vessels and mediate changes in capillary wall permeability through their action over pericytes [Raichle et al. 1975]. Lesions in the locus ceruleus would be expected to cause a release from this tone, which apart from resulting in vasodilatation of the microcirculation would also hinder the transport of water and water-soluble metabolites between circulation and brain parenchyma.

Table 2 Observed and expected numbers of nucleolated nerve cells of locus ceruleus and nucleolar volume of such cells for 41 cases of the various conditions shown. Also given are values of percentage cell loss and reduction in nucleolar volume.

Group	No.	Age (years)	Number of nucleolated nerve cells per 20- μm section		Percentage loss of cells	Nucleolar volume (μm^3)	Percentage reduction in nucleolar volume
			Expected	Observed			
Senile dementia of Alzheimer type	19	84.7 ± 1.1	75.4 ± 0.3	34.8 ± 3.8	54.5***	56.6 ± 1.8	17.7***
Down's syndrome	1	59.0	85.5	4.6	94.6	49.9	27.5
Dementia pugilistica	4	55.2 ± 1.0	87.1 ± 1.0	29.8 ± 1.7	65.8***	51.2 ± 1.4	25.6***
Parkinson's disease	6	65.7 ± 4.1	84.3 ± 2.3	18.1 ± 3.2	78.5***	70.1 ± 3.0	—
Progressive supranuclear palsy	3	56.0 ± 7.5	87.3 ± 3.0	43.0 ± 12.8	50.7*	72.6 ± 3.9	—
Motor neuron disease	8	57.9 ± 2.2	86.1 ± 1.6	88.3 ± 2.6	—	68.2 ± 1.5	—

*, ***, denotes significantly different from expected/control value, $p < 0.05$, < 0.001 , respectively.

In this report we have shown that *atrophy and severe loss of nerve cells from the locus ceruleus are features of Alzheimer's disease, Down's syndrome, and dementia pugilistica*. Severe nerve cell loss is also seen in Parkinson's disease and progressive supranuclear palsy, but without apparently an accompanying reduction in functional capacity of the few that remain. In normal ageing, cell loss is less pronounced (even in extreme old age, only about 25% of cells are lost), and function is well maintained in those that remain. In motor neuron disease, neither change in cell number nor functional capacity is observed.

Biochemical studies of norepinephrine metabolism in these disorders have demonstrated reductions in

(1) activity of those enzymes involved in norepinephrine production in Alzheimer's disease [Cross et al. 1981], Parkinson's disease [McGeer and McGeer 1976], and progressive supranuclear palsy [Jellinger et al. 1980];

(2) tissue norepinephrine levels with age [Winblad et al. 1978, Spokes 1979] in Alzheimer's disease [Winblad et al. 1978, Adolfsson et al. 1979, Mann et al. 1980b], in Down's syndrome [Yates et al. 1981], and in Parkinson's disease [Riederer et al. 1977];

(3) urinary and brain levels of 3 methoxy-4 hydroxyphenyl glycol (MHPG) metabolite in Alzheimer's disease [Winblad et al. 1978, Mann et al. 1980a, Perry et al. 1981] and in Parkinson's disease [Riederer et al. 1977]. By contrast, cases of motor neuron disease show only minimal pathologic alterations in the locus ceruleus, and the CSF norepinephrine level is not decreased [Zeigler et al. 1981]. Any change in norepinephrine metabolism which might occur in dementia pugilistica has not to our knowledge been reported.

Degenerative changes such as loss of RNA, shrinkage of nucleus and nucleolus, and increased frequency of Lewy bodies and neurofibrillary tangles consistently occur within cells of *supraoptic and paraventricular nuclei* in Alzheimer's disease [Mann et al. 1981], in Parkinson's disease [Langston and Forno 1976], and also, but to a more variable extent, in progressive supranuclear palsy [Roy et al. 1974, Tomonaga 1977] and dementia pugilistica [Corsellis et al. 1973]. However, these cells are well preserved in old age [Wulff et al. 1963, Mann et al. 1981], and no alterations in function have been reported in motor neuron disease.

Findings presented here show that extensive pathologic changes, although differing in characteristics and doubtless with different etiologies but all none the less likely to result in a degree of impairment of the functional integrity of the locus

ceruleus/hypothalamus pathways, occur in Alzheimer's disease, Down's syndrome, Parkinson's disease, dementia pugilistica, and progressive supranuclear palsy. Such changes are much less extensive in normally aged individuals and insignificant in motor neuron disease.

A breakdown in function of these pathways in the former group of disorders would presumably impair regulation of blood flow through the microvasculature with alterations in the ability to adequately control the passage of substances between brain and circulation. Through its extensive innervation of the CNS, degeneration of the locus ceruleus could lead to the metabolic disturbances widely seen in other nerve cell types [Mann et al. 1977] and consequently may make an important contribution to the cause of mental deterioration accompanying the disease process in these disorders.

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